

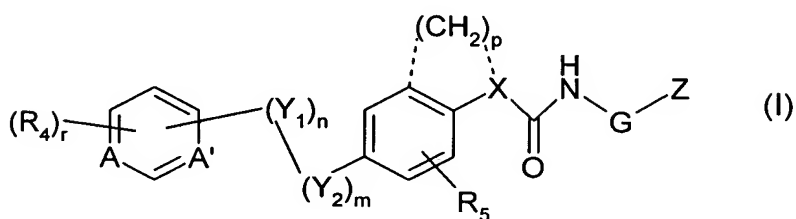
Amendments to the Claims

Listing of Claims:

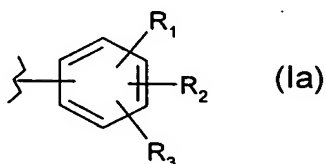
What is claimed is:

Cancel Claims 1-12.

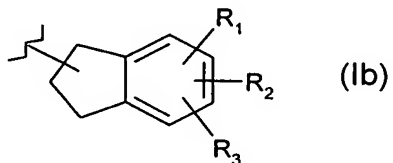
Claim 13 (new): A method of treating RET dependent diseases comprising administering compound of formula I



wherein G is either not present, lower alkylene or C₃-C₅cycloalkylene and Z is a radical of the formula Ia



or G is not present and Z is a radical of the formula Ib



A is CH, N or N→O and A' is N or N→O, with the proviso that not more than one of A and A' can be N→O;

n is 1 or 2;

m is 0, 1 or 2;

p is 0, 2 or 3;

r is 0 to 5;

X is NR if p is 0, wherein R is hydrogen or an organic moiety, or if p is 2 or 3, X is nitrogen which together with (CH₂)_p and the bonds represented in dotted (interrupted) lines (including the atoms to which they are bound) forms a ring,

or

X is CHK wherein K is lower alkyl or hydrogen and p is zero,

with the proviso that the bonds represented in dotted lines, if p is zero, are absent;

Y₁ is O, S or CH₂;

Y₂ is O, S or NH;

with the proviso that (Y₁)_n-(Y₂)_m does not include O-O, S-S, NH-O, NH-S or S-O groups;

each of R₁, R₂, R₃ and R₅, independently of the others, is hydrogen or an inorganic or organic moiety or any two of them together form a lower alkylene-dioxy bridge bound via the oxygen atoms, and the remaining one of these moieties is hydrogen or an inorganic or organic moiety;

and R₄ (if present, that is, if r is not zero) is an inorganic or organic moiety;

or a tautomer thereof;

or a pharmaceutically acceptable salt thereof.

Claim 14 (new): The method according to claim 13, wherein the RET dependent disease is a RET dependent tumour disease.

Claim 15 (new): The method according to claim 14, wherein the RET dependent tumour disease is selected from colon cancer, lung cancer, breast cancer, pancreatic cancer and thyroid cancer.

Claim 16 (new): The method according to claim 15, wherein the cancer is thyroid cancer.

Claim 17 (new): An N-[4-(pyrimidin-4-yloxy)-phenyl]-N'-phenyl-urea derivative selected from the group consisting of the compounds of Examples 34, 51-53, 55, 56 and 72 as described in the description, or a salt thereof.

Claim 18. (new): An N-[4-(pyrimidin-4-yloxy)-phenyl]-N'-phenyl-urea derivative selected from the group consisting of:

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[3-(azetidin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-(3-azetidin-1-ylmethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Azido-pyrimidin-4-yloxy)-phenyl]-N'-(3-azetidin-1-ylmethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-N'-(3-azetidin-1-ylmethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[3-(4-isopropylpiperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[3-(4-isopropylpiperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;

N-[4-(6-Azido-pyrimidin-4-yloxy)-phenyl]-N'-[3-(4-isopropylpiperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;

N-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-N'-[3-(4-isopropylpiperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[3-(4-methylpiperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Azido-pyrimidin-4-yloxy)-phenyl]-N'-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-N'-(3-diethylaminomethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-methylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea trifluoroacetate;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropyl-4-oxy-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea trifluoroacetate;

N-[4-(6-Azido-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-H-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-^{tert}butylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-benzoyloxycarbonyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(N,N-dimethylamino-methyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(N,N-diethylamino-methyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-[(3-dimethylamino-propyl)-methyl-amino-methyl]-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-[(4-cyano-benzyl)-amino-methyl]-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(1-morpholinyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(pyrrolidin-1-yl-amino-methyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-(4-methoxybenzyl)-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(methyl-^{tert}butyl-amino-methyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(azetidin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4,5-dimethylimidazol-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(2-methylimidazol-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(2,4-dimethylimidazol-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-ethylpiperazin-1-ylmethyl)-3-methyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-ethylpiperazin-1-ylmethyl)-phenyl]-urea;

1-(4-[1,4']Bipiperidinyl-1'-yl-3-trifluoromethyl-phenyl)-3-[4-(6-chloro-pyrimidin-4-yloxy)-phenyl]-urea;

1-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-3-{4-[4-(2,2-dimethyl-propyl)-piperazin-1-ylmethyl]-3-trifluoromethyl-phenyl}-urea;

1-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-3-{4-[4-(2,2-dimethyl-propyl)-piperazin-1-yl]-3-trifluoromethyl-phenyl}-urea;

1-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-3-[4-(1-methyl-piperidin-4-ylmethoxy)-3-trifluoromethyl-phenyl]-urea;

1-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-3-[4-(1-methyl-piperidin-4-yloxy)-3-trifluoromethyl-phenyl]-urea;

N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-{4-[2-(4-ethyl-piperazin-1-yl)-ethyl]-3-trifluoromethyl-phenyl}-urea;

3-{3-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-ureido}-5-trifluoromethyl-benzamide;

3-{3-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-ureido}-5-trifluoromethyl-benzamide;

3-{3-[4-(6-Azido-pyrimidin-4-yloxy)-phenyl]-ureido}-5-trifluoromethyl-benzamide;

3-{3-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-ureido}-5-trifluoromethyl-benzamide;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-(3-aminomethyl-5-trifluoromethyl-phenyl)-urea;

3-{3-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-ureido}-N-methyl-5-trifluoromethyl-benzamide;

3-{3-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-ureido}-N-methyl-5-trifluoromethyl-benzamide;

3-{3-[4-(6-Azido-pyrimidin-4-yloxy)-phenyl]-ureido}-N-methyl-5-trifluoromethyl-benzamide;

3-{3-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-ureido}-N-methyl-5-trifluoromethyl-benzamide;

N-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-(3-methylaminomethyl-5-trifluoromethyl-phenyl)-urea;

N-[4-(2-Amino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(2-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-isopropylpiperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(2-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(dimethylamino-methyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(2-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-dimethylamino-methyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(2-Methylamino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-tert-butylpiperazinyl-methyl)-3-trifluoromethyl-phenyl]-urea;

N-[4-(2-Amino-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-tert-butylpiperazinyl-methyl)-3-trifluoromethyl-phenyl]-urea;
 1-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-3-[3-(6-methyl-pyridin-2-yl)-5-trifluoromethyl-phenyl]-urea;
 1-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-3-(4-pyridin-2-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-3-(4-pyridin-3-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-3-(4-pyridin-4-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Amino-pyrimidin-4-yloxy)-phenyl]-3-[4-(6-methyl-pyridin-2-yl)-3-trifluoromethyl-phenyl]-urea;
 1-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-3-(4-pyridin-2-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-3-(4-pyridin-3-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-3-(4-pyridin-4-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Methylamino-pyrimidin-4-yloxy)-phenyl]-3-[4-(6-methyl-pyridin-2-yl)-3-trifluoromethyl-phenyl]-urea;
 N-[4-(6-Chloro-pyrimidin-4-yloxy)-phenyl]-N'-[4-(4-ethylpiperazin-1-ylmethyl)-3-chloro-phenyl]-urea;
 1-[4-(2-Amino-pyrimidin-4-yloxy-phenyl)-3-(4-piperazin-1-ylmethyl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(2-Methylamino-pyrimidin-4-yloxy-phenyl)-3-(4-piperazin-1-ylmethyl-3-trifluoromethyl-phenyl)-urea;
 N-(6-{4-[3-(3-Trifluoromethyl-phenyl)-ureido]-phenoxy}-pyrimidin-4-yl)-acetamide;
 N-(6-{4-[3-(4-Morpholin-4-yl-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyrimidin-4-yl)-acetamide;
 6-(4-{3-[4-(4-Ethyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-ureido}-phenoxy)-pyrimidin-4-yl]-carbamic acid methyl ester;
 1-[4-(2-Acetylamino-pyrimidin-4-yloxy)-phenyl]-3-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 3-[3-(4-{6-[4-(tert-Butyl-dimethyl-silanyloxy)-phenylamino]-pyrimidin-4-yloxy}-phenyl)-ureido]-5-trifluoromethyl-benzamide;
 1-(3'-Chloro-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-methyl-phenyl}-urea;
 1-(3'-Bromo-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-methyl-phenyl}-urea;

1-(4'-Chloro-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-methyl-phenyl}-urea;
 1-(4'-Bromo-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-methyl-phenyl}-urea;
 1-(3'-Chloro-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-trifluoromethyl-phenyl}-urea;
 1-(3'-Bromo-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-trifluoromethyl-phenyl}-urea;
 1-(4'-Chloro-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-trifluoromethyl-phenyl}-urea;
 1-(4'-Bromo-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-2-trifluoromethyl-phenyl}-urea;
 1-(3'-Chloro-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-phenyl}-urea;
 1-(4'-Chloro-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-phenyl}-urea;
 1-(4'-Bromo-2-trifluoromethyl-biphenyl-4-yl)-3-{4-[2-(4-dimethylamino-butylamino)-pyrimidin-4-yloxy]-phenyl}-urea;
 1-{4-[2-(3-Methoxy-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-[4-(4-methyl-piperazin-1-ylmethyl)-3-trifluoromethyl-phenyl]-urea;
 1-2-Methyl-4-{2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yloxy}-phenyl)-3-(3-trifluoromethyl-phenyl)-urea;
 1-{4-[6-(5-Chloro-2-methoxy-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;
 1-{4-[6-(4-Methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;
 1-[4-(6-Dimethylamino-pyrimidin-4-yloxy)-phenyl]-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;
 N,N-Dimethyl-4-(6-{4-[3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyrimidin-4-ylamino)-benzamide;
 1-{4-[6-(2-Methoxy-5-methyl-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;
 1-{4-[6-(2-Methoxy-5-nitro-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;
 1-{4-[6-(2,5-Dimethoxy-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;

1-{4-[6-(2,5-Dimethoxy-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;

N,N-Diethyl-4-methoxy-3-(6-{4-[3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyrimidin-4-ylamino)-benzenesulfonamide;

1-{4-[6-(2-Methoxy-phenylamino)-pyrimidin-4-yloxy]-phenyl}-3-(4-morpholin-4-yl-3-trifluoromethyl-phenyl)-urea;

or a salt thereof.

Claim 19 (new): A pharmaceutical composition comprising an N-[4-(pyrimidin-4-yloxy)-phenyl]-N'-phenyl-urea derivative selected from the group consisting of the compounds of Claim 17.

Claim 20 (new): A pharmaceutical composition comprising an N-[4-(pyrimidin-4-yloxy)-phenyl]-N'-phenyl-urea derivative selected from the compounds of Claim 18.

Claim 21 (new): A method of treating a protein kinase dependent disease depending on any one or more of the protein tyrosine kinases selected from c-Abl, Bcr-Abl, Flt-3, RET, VEGF-R and/or Tek comprising administering a compound according to claim 17.

Claim 22 (new): A method of treating a protein kinase dependent disease depending on any one or more of the protein tyrosine kinases selected from: c-Abl, Bcr-Abl, Flt-3, RET, VEGF-R and/or Tek, comprising administering a compound according to claim 18.

Claim 23 (new): A method according to claim 21 wherein the protein kinase is Flt-3.

Claim 24 (new): A method according to claim 22 wherein the protein kinase is Flt-3.